REMARKS

A. Status of the Claims

Claims 1-3 were pending at the issuance of the instant Office Action. Claims 1-3 are rejected in the instant Office Action. No claims are amended, added, or canceled herein. Applicants thank the Examiner for the previous consideration of our submissions.

B. Interview Summary

Applicants extend their thanks for the phone interview on January 14, 2010. Participating in the interview were Examiner Zohreh Fay and Jason Derry. The art cited in the instant Office Action was discussed in view of data that were presented in Applicants' Application Serial No. 10/498,721. The data demonstrated that not all compounds which are considered to have superoxide dismutase activity are effective for treating retinal diseases. It was agreed that submitting the Declaration that was submitted in Application Serial No. 10/498,721 may provide evidence that the present claims are not obvious in view of the art cited in the instant Office Action. Applicants are submitting the Declaration as Exhibit A, attached hereto, and provide below a more detailed explanation as to how the data provide evidence of that the present claims are patentable over the cited art.

C. Rejections under 35 U.S.C. § 103(a)

Claims 1-3 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Malfroy-Camine *et al.* (6,064,188) in view of Winkler *et al.* (Molecular Vision 1999). The rejection is based on an unsubstantiated proposition allegedly taught by Winkler *et al.* In particular, the Action asserts that Winkler *et al.* teach the effect of oxidation in relation to macular degeneration. The Action relies on Winkler *et al.* to support the assertion that the use of any superoxide dismutase compound for treating retinal diseases would be obvious. The Action also asserts that Gurler *et al.* and Kimura *et al.* "emphasize the effect of oxidative damage in diabetic retinopathy and ... show that the polymorphism manganese superoxide dismutase gene is associated with exudative age related macular degeneration" (Office Action, page 2). Applicants respectfully traverse these assertions.

Regarding the proposition based on Winkler *et al.*, as stated in MPEP 2143.02(II): "obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness" (citing *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)). Applicants submit that the teachings of De La Paz and Delcourt (discussed in Applicants' Responses submitted August 1, 2007, October 1, 2007, January 6, 2009, April 4, 2009, and August 26, 2009) provide evidence that one of skill in the art would not necessarily have expected that superoxide dismutase compounds could be used to treat macular degeneration. As pointed out previously, De La Paz and Delcourt conclude that there is no significant association between disease severity of AMD and superoxide dismutase activity, and that high levels of erythrocyte superoxide dismutase activity were not associated with late AMD and early signs of AMD. Winkler *et al.* do not provide any evidence to the contrary. Thus, the Action cannot rely on Winkler *et al.* to support the generalization that those of skill in the art recognized that superoxide dismutase plays a role in preventing oxidative damage caused by macular degeneration.

The Kimura reference from the specification of the present patent application (*Am. J. Ophthalmol* **2000**, *130*, 769-773) reported that in a Japanese cohort, a significant positive correlation existed between wet AMD and a mutation in the SOD-2 gene called V16A. This mutation corresponded to a valine/alanine substitution in the targeting sequence of the enzyme. However, the Kimura results were not universally substantiated at the time they were published, and subsequent reports have indicated that the conclusions may not be valid. For example, Esfandiary *et al.* (Esfandiary *et al.*, *Br. J. Ophthalmol.* **2005**, *89*(4), 470-474) have disclosed that in a population from Northern Ireland there was no statistically significant correlation found between the V16A SOD-2 gene mutation and wet AMD. Furthermore, Gotoh *et al.* reported (Gotoh *et al.*, *Am. J. Ophthalmol.* **2008**, *146*(1), 146) that the V16A SOD-2 gene mutation was protective against wet AMD in a Japanese population. In these 3 different literature reports, the SOD-2 gene V16A mutant has been described as risk-increasing, irrelevant, and risk-decreasing, with respect to wet AMD development. In a review article summarizing these findings among others, Kondo *et al.* (Kondo *et al.*, *Mol. Vis.* **2009**, *15*, 1819-1826) stated that "A large number of additional candidate susceptibility genes have been studied, but findings from most studies are inconclusive because of a lack of

consistent replication." Thus, one of skill in the art could not determine whether there was any causal relationship between this SOD-2 gene mutation and wet AMD risk based on these references.

The Gurler reference mentioned in the specification of the present patent application (Gurler, *et al.*, *Eye(London)* **2000**, *15 (Pt. 5)*, 730-735) disclosed that while there was a decreased serum vitamin C concentration in diabetic retinopathy (DR) patients as compared to normals, there was no statistically significant difference in erythrocyte SOD enzyme concentration between the two groups. This reference implies that the enhanced oxidative stress in diabetic retinopathy patients is characterized by a deficiency in ascorbate and not the SOD enzyme. The only clear teaching from Gurler is that ascorbate supplementation might be advisable to correct this deficiency. There is no suggestion from Gurler that intervention with the SOD enzyme or a mimic thereof would have any impact on this pathological feature.

Those of skill in the art at the time the instant application was filed understood the general proposition that different anti-oxidants might be expected to have widely divergent therapeutic utilities. As mentioned in Applicants' previous response, the Winkler reference itself discloses that superoxide (half life of 10^{-5} seconds) is less reactive than either singlet oxygen (half life of 10^{-6} seconds) or hydroxyl radical (half life of 10^{-9} seconds); the latter two are described as "a particular destructive oxygen metabolite" (p. 34) and "one of the more reactive of all the free radicals" (p. 34). Thus it is not clear that a SOD mimic that inefficiently reacts with singlet oxygen or hydroxyl radical will have therapeutic benefit on AMD- and DR-related pathological oxidative stress. Furthermore a SOD mimic will produce hydrogen peroxide as an obligatory by-product. Since Winkler (figure 13, p. 40) discloses that peroxide is toxic RPE cells, and since several previously cited references (*e.g.*, Liles *et al.*, *Arch. Ophthalmol.* **1991**, *109*(9), 1285-1288; Yildrium *et al.*, *Ophthalmologic* **2004**, *218*(3), 202-206) have shown a correlation between reduced expression of peroxide-detoxifying catalase enzyme expression and AMD in humans, it is again not clear from the art that a SOD mimic would have therapeutic benefit against AMD.

To further demonstrate that not all compounds that are reported to have SOD activity act the same, Applicants are providing herewith a Declaration from Dr. Robert J. Collier, Jr.

Compounds") are inactive in a blue light photo-oxidative induced retinopathy model, whereas the SOD mimics of Application Serial No. 10/498,721 are active in the same model. Therefore, the evidence provided in the Declaration clearly demonstrates that not all compounds reportedly having SOD activity will necessarily act the same, and that not all are useful for treating macular degeneration, diabetic retinopathy, or retinal edema. Consequently, Winkler *et al.* cannot stand for the proposition that any SOD mimic will be useful for treating such disorders.

In light of the foregoing arguments, Applicants submit that the claims are not obvious in view of the cited references. Consequently, Applicants respectfully request that the obviousness rejection be withdrawn.

C. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Jason J. Derry, #50,692/
Jason J. Derry, Ph.D.
Reg. No. 50,692
Attorney for Applicants

ALCON RESEARCH, LTD.
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
817-615-5330

Date: February 25, 2010

Exhibit A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Peter G. Klimko
Robert J. Collier, Jr.
Mark R. Hellberg

Serial No.: 10/498,721 (Conf #7892)

Filed: June 14, 2004

For: SUPEROXIDE DISMUTASE MIMICS FOR THE TREATMENT OF OCULAR DISORDERS AND DISEASES

Group Art Unit: 1612

Examiner: Fay, Z.

Atty. Dkt. No.: 2338 US F

DECLARATION UNDER 37 C.F.R. §1.132

1. I, Robert J. Collier, Jr., am one of the above named inventors in the above-identified U.S. patent application.

2. I have a Ph.D. in Psychology from The Center for Visual Sciences, Department of Psychology, University of Rochester, Rochester, N.Y.

3. At the present time, I am Associate Director – Retina Discovery at Alcon Laboratories. My responsibilities at Alcon include Retina Drug Discovery. I have extensive knowledge in the field of retina research in which I have been practicing since 1976.

4. I am familiar with the present application and the Office Action dated June 5, 2009. In the Office Action, the Examiner states that "Crapo et al. was cited to show that structurally similar compounds having superoxide dismutase activity have been previously used for the treatment of macular degeneration" (Office Action, page 2). I respectfully disagree with the Examiner's position that the compounds disclosed in Crapo ("the Crapo Compounds") are similar in structure to the compounds of the instant claims, since the Crapo Compounds are porphyrin-containing oxidant scavengers while the compounds of the instant claims are

nonpeptidyl superoxide dismutase mimetics. Further, the Crapo Compounds and the compounds of the instant claims differ mechanistically, such that one of skill in the art would not necessarily have expected the compounds of the instant claims to be effective for any alleged use of the Crapo Compounds. The following data were generated under my supervision to demonstrate that the differences between the Crapo Compounds and the compounds of the instant claims are significant, and that one of skill in the art would not have considered it obvious to the compounds of the instant claims for place of the Crapo Compounds for any purpose.

5. We evaluated the effect of blue-light exposure on vehicle-dosed rats, as compared to rats treated with different concentrations of Mn(III) tetrakis (4-benzoic acid)porphyrin (Mn-TBAP) (1 to 20 mg/kg, intraperitoneal (IP) delivery). Mn-TBAP is a compound disclosed in the Crapo patent (US Patent Number 6,127,356) as one of the specific mimetics suitable for use in the methods disclosed in the Crapo patent (see column 16, lines 24-25). Albino rats were dark adapted for 24 hours prior to induction of photochemical lesions with blue light (3.1×10^3 mW/cm^2, λ=450 nm, half-amplitude bandpass = 425–475 nm) for 6 hours. Rats were allowed to recover for 5 days in darkness prior to evaluating retinal function in anesthetized rats by recording the electroretinogram (ERG), the electrical response of the retina generated by a brief flash of light. ERGs recorded from a platinum-iridium wire loop electrode positioned on the cornea were elicited by viewing a ganzfeld. Electrical responses to a single, bright, visible-light flash were digitized to analyze temporal characteristics of the waveform and maximum response amplitude. The amplitude of the a-wave was measured as the voltage difference between the baseline recorded prior to the flash and the trough of the a-wave. The b-wave was measured as the voltage difference between the peak of the b-wave and trough of the a-wave.

6. Blue-light exposure to vehicle-treated rats for 6 hours resulted in a significant diminution of the ERG response amplitude (t-Test, $p<0.05$) compared to controls when measured after a 5-day recovery period (Exhibit 1). Blue-light exposure resulted in a 40% reduction in the maximum a-wave response amplitude in vehicle-dosed rats compared to controls. This reduction in a-wave amplitude results from damage to photoreceptors and retinal pigment epithelium cells.

Light microscopic examination of vehicle-dosed retinas demonstrates thinning of the outer nuclear layer (due to photoreceptor loss, primarily by apoptosis) and thinning/ loss of retinal pigment epithelium cells. ERG b-wave response amplitudes, a measure of inner retina function, in particular, on-bipolar cells, were also reduced 44% due to photoreceptor/ RPE damage. No significant lesions were found in the inner nuclear layer or ganglion cell layer.

7. Treatment with Mn-TBAP did not provide significant protection of retinal function compared to vehicle-dosed blue-light exposed rats (Exhibit 1). Maximum ERG a-wave amplitudes were depressed between 63% (5 mg/kg dosed rats) to 41% (10 mg/kg dosed rats) compared to normal response amplitudes, while maximum b-wave response amplitudes were depressed between 76% (5 mg/kg dosed rats) to 42% (10 mg/kg dosed rats).

8. For comparison, treatment with compound 4 from the instant application = AL-37797 (1 to 20 mg/kg, IP delivery), a nonpeptidyl superoxide dismutase mimetic, is shown in Exhibit 2. In albino rats dosed with 10 or 20 mg/kg AL-37797, significant protection ($p<0.05$) was measured for ERG a- and b-wave response amplitudes and ERG responses were not statistically different than controls ($p>0.05$). AL-37797 demonstrated the ability to completely ameliorate changes in photoreceptor and RPE structure and function.

9. Accordingly, Exhibits 1 and 2 show that the Crapo Compounds are not effective for treating macular degeneration, diabetic retinopathy, or retinal edema, whereas the compounds of the instant invention are effective for such treatments based on the results obtained with the blue light photo-oxidative induced retinopathy model described above.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and any such willful false statement may jeopardize the validity of the application or

any issuing thereon.

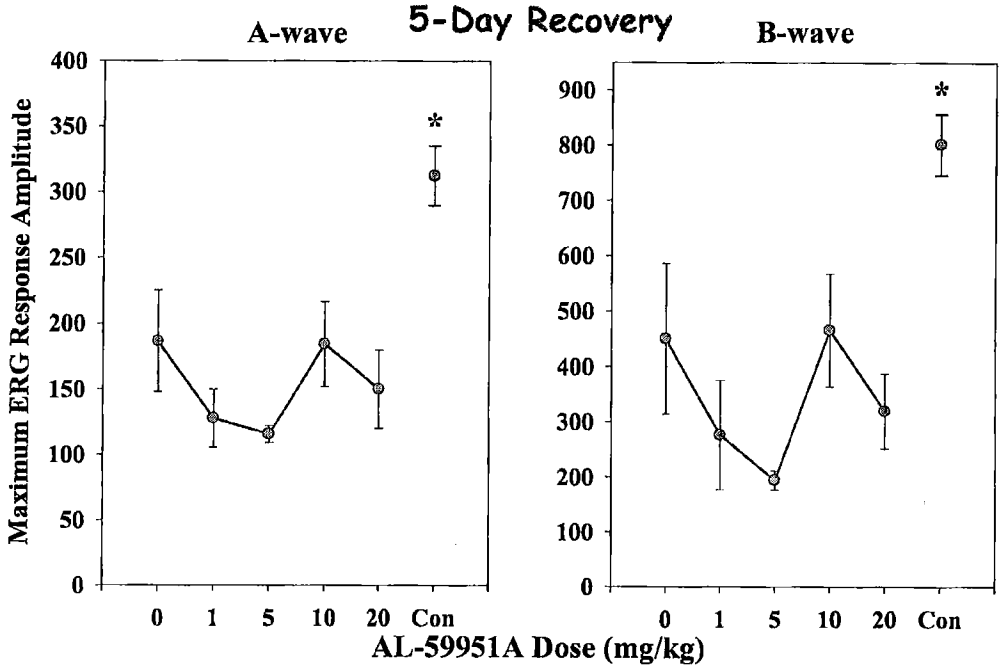
Date: 9-4-2009

Robert J. Collier, Jr.

Robert J. Collier, Jr.

Exhibit 1: ERG response amplitudes from AL-59951A (1 to 20 mg/kg) treated rats were not statistically higher than responses from vehicle-dosed rats.

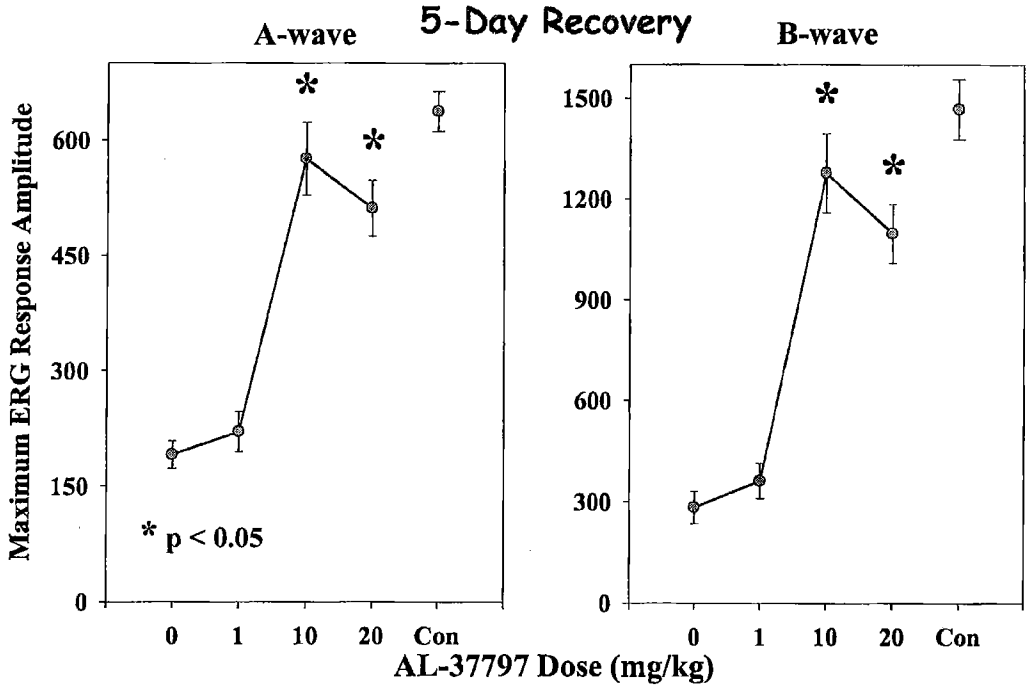
Evaluation of AL-59951A (Mn-TBAP, SOD Stimulant) in the Rodent Acute Photic Injury Model



Response amplitude higher than Vehicle ($p<0.05$)

Exhibit 2: ERG response amplitudes from AL-37797A (10 and 20 mg/kg) treated rats were statistically higher than responses from vehicle-dosed rats and were not statistically different from responses measured in control rats.

Evaluation of AL-37797A in the Rodent Acute Photic Injury Model



Response amplitude higher than Vehicle ($p<0.05$) and not different than control.